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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,485	12/08/2000	Erwin Ludo Roggen	6067.200-US	2466

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NOVOZYMES NORTH AMERICA, INC.
500 FIFTH AVENUE
SUITE 1600
NEW YORK, NY 10110

EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,485	ROGGEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/23/04 has been entered.

Status of Claims

Claims 1-68 have been cancelled.

Claims 69-70 are pending and under examination.

Specification

The use of the trademark Savinase at page 61, line 26 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any

manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA encoding a Savinase or Savinase library enzyme, does not reasonably provide enablement for the broadly claimed method using a gene encoding a diversified library of protein variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons advanced in the last Office action.

Response to Arguments

Applicants argue that a patent need not teach and preferably omits what is well known in the art. It is argued that proteins and DNA sequences encoding same are well known in

the art. At pages 30-38, applicants state that the specification describes numerous proteins for use in the claimed method. It is routine for one of ordinary skill in the art to generate libraries of variants of a protein, as described at e.g., pages 40-44.

In response, it is not controverted that there are myriads of proteins and DNA known in the art. The issue is the applicability of these huge compounds to the instant claimed method of selecting, not the existing proteins, but variants thereof using the claimed steps. Contrary to applicants' statement generation of libraries of protein variants can hardly be considered routine. The high unpredictability of screening library of proteins, let alone variants, is notoriously known in the art. One of the greatest challenges still faced by skilled artisan is the true representation of a compound in a diverse library, specifically expression in a host cell. The nature of applicants' invention is so complex and unpredictable. A library of protein variants used in the method will include millions of complex or combinations of different proteins. The claims do not impose any limitations as to the library e.g., size, length, modifications, its insertion and/or deleterious effects on a host cell and other unpredictable effects and/or factors. Without such limitations, the method amounts to nothing but an

invitation to experiment. All studies or experiments done to date on the art are done on a case-to-case basis. Even a simple condition such as temperature, sampling method or sample size or concentration is known to affect the study on hand. The experiments provided in the specification are directed to a single library with no known functionality. It uses different terminologies that are confusing as it is not apparent as to which one is being referred to. The results are alleged to be given in the drawing Figures. However, there is no explanation of the results in the drawings and it is not clear as to the numbers provided therein. Also, the Example relies on numerous trademark products; the components therein are not even described. For the reasons given above, the enabling disclosure is not commensurate in scope with the protection being sought. In re Din-Nguyen. The broad claimed method is not commensurate with the specific enabling disclosure in the specification.

Claims 69-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention for reasons advanced in the last Office action.

Response to Arguments

Applicants employ the same reasoning above, herein. The written description and non-enabling disclosure are two different issues. Nevertheless, the rebuttal above is also relied herein. Additionally, the rejection in the last Office action is reiterated below.

The specification fails to provide an adequate written description of a method for selecting a variant protein with reduced immunogenecity by screening using competitive ELISA assay. In conjunction, there is no description in the specification as to a diverse DNA library of genes that encodes a variant protein. It does not describe how a diverse DNA library of genes is generated, the source of the diverse kinds of genes and/or identification of the genes for library formation. The description, particularly the EXAMPLES, which details the method used by applicants, describes a single, specifically known library, Savinase. Savinase is a trademark for a library. It is not readily apparent from the trademark or trade name as to the proper identity of the particular library material or product. The trademark does not identify the type of genes present in said trademark or the protein variants

encoded by the genes or the means by which it is diversified. The EXAMPLES does not further describe screening by competitive ELISA assay. There are no steps for said competitive ELISA assay or the components present for a competitive assay. More importantly, there are no steps as to the selection or screening based on reduced immunogenecity rather, than the binding effect of the variants to an antibody.

The claimed method step (d) of preparing samples of each cell culture is not supported in the as-filed specification. Applicants point out support at page 45, lines 15-29. However, the cited section presents a different concept than the presently amended limitation. The original specification describes a sampling from the cultured host cells and not a step of preparing samples of each cell culture as presently claimed.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In view of the amendments to the claims, the rejection in the last Office action no longer applies.

Claim 69, as amended, is confusing as to the step method of "preparing samples of each cell culture". Applicants in the 2/23/04 Response cite e.g., page 45, lines 15-29. A review of the cited section does not positively support a method of making. Rather, a method of sampling, appropriately so, a sample in the cultured host cells.

Double Patenting

Claims 69 and 70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-73 of copending Application No. 09/417,608('608 application)(now USP 6,686,164). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons set forth in the last Office action.

Response to Arguments

Applicants argue that the claims of the '608 application now an issued patent and the '173 application do not use competitive ELISA as recited in the present claims.

In reply, attention is drawn to claim 17 of the issued Patent 6,686,164('608 application), which recites the competitive ELISA method. [It is noted that applicants have

filed several applications having one or more common inventors that appears to claim the same invention except worded differently. Applicants are required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 69 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Lowman et al (USP 5,994,511).

Lowman discloses a method for selecting novel binding polypeptides comprising: a) constructing a replicable expression vector comprising a first gene encoding a polypeptide, a second

gene encoding at least a portion of a natural or wild-type phage coat protein wherein the first and second genes are heterologous, and a transcription regulatory element operably linked to the first and second genes, thereby forming a gene fusion encoding a fusion protein; b) mutating the vector at one or more selected positions within the first gene thereby forming a family of related plasmids; c) transforming suitable host cells with the plasmids; d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein; e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that no more than a minor amount of phagemid particles display more than one copy of the fusion protein on the surface of the particle; f) contacting the phagemid particles with a target molecule so that at least a portion of the phagemid particles bind to the target molecule; and g) separating the phagemid particles that bind from those that do not. Preferably, the method further comprises transforming suitable host cells with recombinant phagemid particles that bind to the target molecule and repeating steps d) through g) one or more times. At col. 19, lines 10-11 Lowman discloses the enzymes subtilisin, trypsin and other serine

proteases that can be used in the method. The competitive binding assay is described at col. 56. See e.g., Example 4 at col. 73 up to col. 82, line 31, which provides a detail description of the method. Accordingly, the specific process steps of Lowman, which employs specific components therein fully, meet the broad claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 69 and 70 are rejected under 35 U.S.C. 103(a) as being obvious over Jespers et al (J. Mol. Biol.).

Jespers discloses a method of screening for a protein variants, Sak antigens, comprising making a library of mutated Sak antigens displayed on the surface of filamentous phage (transformation into host cells, as claimed) that results in a reduced antibody binding without altering the function of the protein, page 713, col. 1. A positive and negative selection steps (sampling as claimed) against immobilized monoclonal and polyclonal antibodies

are used to delineate dominant antigenic determinants of Sak. In addition, mutated Sak-phages are selected from reduced antibody recognition with retention of plasminogen binding activity, (paragraph bridging pages 713-714). See the detailed steps disclosed at page 714, col. 1 up to page 716, col.2. Jespers does not disclose a competitive ELISA for detecting binding as claimed. However, Sosin at [0033] discloses that to determine whether the library screening has yielded a complete inventory of the allergen-specific IgEs present in patient serum, an immunocompetition assay can be performed. Pooled recombinant Fabs would be preincubated with immobilized allergen. After washing to remove unbound Fab, the immobilized allergen would then be incubated with patient serum. After washing to remove unbound serum proteins, incubation with a reporter-coupled secondary antibody specific for IgE Fc domain would be performed. Detection of bound reporter would allow quantitation of the extent to which serum IgE was prevented from binding to allergen by recombinant Fab. The level of uncompeted serum IgE binding would be determined using allergen, which had not been preincubated with Fab or had been incubated with nonsense Fab. It would have been obvious to one having ordinary skill in the art at the time the invention was made to use a competitive ELISA assay in the method of Jespers in the manner as taught by Sosin. Sosin provides the

motivation for using immunocompetition i.e., complete inventory for the presence of a protein (in Sosin's case, IgE) in a patient serum. Furthermore, as evident from the newly submitted reference, competitive ELISA is one of the conventional methods used in immunoassay.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
May 1, 2004